LACTIC ACID

CAS # 50-21-5
HPV CHEMICAL # 50215

TEST PLAN JUSTIFICATION

TEST PLAN

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1. TEST PLAN JUSTIFICATION FOR LACTIC ACID (CAS# 50-21-5)

It is good to mention that PURAC America Inc. was committed to send in data on CAS number 50-21-5, which is the racemic form of lactic acid. However, PURAC and most other suppliers of lactic acid, only manufacture the natural form of lactic acid, L(+) lactic acid. Most data available in public literature are about the L(+) form only and most studies done have been performed with L(+) lactic acid. Therefor it made sense to base the files on L(+) lactic acid (CAS# 79-33-4). This document has been written to summarise the findings of the robust summary for L(+) lactic acid, to describe other relevant literature and to explain why no additional testing is proposed for L(+) Lactic Acid.

❖ Introduction

Lactic acid (2-Hydroxypropionic acid) was discovered in 1780 by the Swedish chemist Scheele. L(+) lactic acid is an organic acid which is an essential part of human metabolism. Also many different animals and micro-organisms need L(+) lactic acid in their metabolism.

L(+) lactic acid is an organic acid with a long history in food. E.g. in fruits it is formed through fermentation. Nowadays, L(+) lactic acid and its derivatives are maily used in the food industry e.g. for preservation and flavouring purposes. L(+) lactic acid has a GRAS status and it has a European food additive approval (E 270). L(+) lactic acid has been approved in many other countries as a food additive.

On top of that, there is an increased number of applications in the pharmaceutical, cosmetic and chemical industry. The world production of L(+) lactic acid is around 100,000 tons per year. Major part of this volume is manufactured by fermentation of various carbohydrate sources and subsequent down stream purification. Some lactic acid (mainly the racemic form) is manufactured by synthesis and purification.

Every human being "produces" and metabolises daily about 125 - 150 grams of L(+) lactic acid. Relative contribution of the L(+) lactic acid consumed to the human metabolism is relatively very low. Consumption of 50,000 tons of L(+) lactic acid (half of the global production) across the USA would lead to an additional L(+) lactic acid intake / metabolism of 550 micrograms / person / day, being 0,45% of the normal daily metabolism.

❖ Physical - chemical properties

L(+) lactic acid is a clear to slightly yellowish liquid, typically supplied to formulators in a 88 - 92% concentration. The physical and chemical properties of L(+) lactic acid have been well described. The boiling point and melting point, vapour pressure, water solubility and partition coefficient are very well known. Much information on lactic acid e.g. can be found in the book "Lactic acid, properties and chemistry of lactic acid and derivatives" by C.H. Holten (1971).

❖ Environmental fate

Photodegradation

The photochemical oxidation of Lactic Acid is discussed in the handbook by C.H. Holten, mentioned above. Berthelot and Gaudechon, who irradiated calcium lactate and ethyl lactate, made the first observation that lactic acid is photosensitive in 1910. They observed decomposition with the formation of a gas containing carbon monoxide, carbon dioxide, hydrogen and methane.

Stability in water

From the robust summary it is clear that lactic acid in an aqueous environment will have a very high stability (between 79 and 98 years).

Transport between compartments

If discharged into water, L(+) lactic acid will stay predominantly in the water compartment. As L(+) lactic acid is not volatile and as it has a high biodegradation rate, transport between environmental compartments (air and soil / water) is no issue.

Biodegradation

The biodegradability of L(+) lactic acid was examined using the Biological Oxygen Demand (BOD) and the Chemical Oxygen Demand (COD). Testing was done according EC test guidelines and OECD GLP principles.
The BOD_5 was found to be 0.45 mg O_2/mg and the BOD_{20} was found to be 0.60 mg O_2/mg. The COD was 0.90 mg O_2/mg. These figures show a degradation of 50% after 5 days and 67% after 20 days.
Thus L(+) lactic acid is highly biodegradable. L(+) lactic acid is widely recognised as being readily biodegraded in the environment as it is both a nutrient and a metabolite for microbes. Accordingly, L(+) lactic acid is not expected to biopersist or bioaccumilate in the environment.

❖ Ecotoxicity

Acute toxicity to aquatic plants

One study exhibits the very low toxicity of L(+) lactic acid in Algae Selenastrum Capricornutum, as the Observed No Effect Concentration was found to be 1.9 g/l

Aquatic toxicity to invertebrates

In two other studies, L(+) lactic acid also exhibits very low toxicity to aquatic organisms. Two studies have been done to establish the toxicity of L(+) lactic acid to Daphnia Magna. Both studies covered a period of up to 48 hours. The 48 hours No Observed Effect Concentration ranged from 180 mg/L to 320 mg/L.

Acute toxicity to fish

Three studies have been done to establish the toxicity of L(+) lactic acid in Salmo Gairdneri (rainbow trout), Lepomis Macrochirus (bluegill sunfish) and to Brachydanio Rerio. These studies covered a period of up to 96 hours. The No Observed Effect Concentration ranged from 56 mg/l to 320 mg/l.

❖ Health Endpoints

Acute Oral Toxicity

As mentioned, L(+) lactic acid is an essential link in the mammalian metabolism. Therefor it will be clear that L(+) lactic acid is practically non-toxic. This is also shown by the LD_{50} values of L(+) lactic acid obtained after various routes of administration in mammals.

The oral LD50 was found to be a little below 5 grams / kg bodyweight in male rats and a little over 3,5 grams/kg body weight in female rats. Several non-critical symptoms were recorded at a dose level of 5 g/kg bodyweight.

Acute Dermal Toxicity

In a prior test conducted in 1986, corrosive effects were observed in albino rabbits exposed to 88% L(+) lactic acid. However, it is well established that for many compounds the skin of the rabbit is substantially more permeable to topically applied compounds than is the human skin and that permeability is, in turn, directly related to potential irritive effects. Because of that TNO (Dutch Institute for Applied Science) concluded that the test using albino rabbits did not adequately predict the probable effect of 88% unbuffered L(+) lactic acid on human skin and that re-testing with a more representative model was indicated. A number of comparative studies *in vivo* on percutaneous absorption have shown the skin of the pig to be most relevant to the skin of man. In this regard it is worth to mention that both the 1981 and 1992 versions of OECD guideline 404 state that while the albino rabbit is the preferred test animal, "several mammalian species may be used". The guideline leaves the choice of species to the researcher's sound scientific judgement.
Accordingly, TNO selected pigs as a more appropriate and representative animal model for re-testing of L(+) lactic acid. In pigs L(+) lactic acid did not give any serious skin irritation.

On basis of the test results provided, the US-DOT (Department of Transport) came to the following conclusion: "Based on the definition of "corrosive materials" at 49 CFR 173.136, test criteria to determine the packing group of class 8 material at 49 CFR 173.137, and test data and other information submitted, it is the DOT's opinion that lactic acid as tested is not a corrosive material.

In-vitro genotoxicity

An Ames test was done to establish the in-vitro genotoxicity. Results were negative. Also, the nature of L(+) lactic acid (human metabolite) does make additional testing not necessary.

Repeated dose toxicity

Four studies have been reported in the robust summary about repeated dose toxicity, three in rats and one in hamsters.

- 90 days - rat - 4ml lactic acid 10% on 20 g of meal
No differences in appearance, gross observations at necropsy, or organ weights were observed between the test and control animals. Changes in blood carbon dioxide were slight.

- 13 weeks - rat - 886 mg/kg bodyweight.
There were no significant gross observations, with the exemption of mild skin irritation. Absolute brain weight and kidney-to-body weight rations were increased for test animals. No lesions were seen observed at necropsy or at microscopic examination

- 14 weeks - hamster - water containing up to 0.05% lactic acid ad libitum
Three groups showed same growth and health..

- 13 weeks - rats - 0,3 to 5% calcium lactate in food.
A 10% decrease in body weight gain. All animals survived, some haematological and biochemical parameters changed, but no severe lesions were found in microscopic examination.

Reproductive toxicity / In-vivo genotoxicity / Developmental toxicity

It has been mentioned that L(+) lactic acid is an essential part of the human metabolism. Every human being makes and metabolises about 125 - 150 grams of L(+) lactic acid each

day. Although studies have not been done to investigate reproductive toxicity, in-vivo genotoxicity or developmental toxicity, it will be clear that L(+) lactic acid has such a low potential risk (~ zero) that studies will not be needed.

❖ Conclusion

The information given in the robust summary will be adequate to establish the environmental fate and toxicity of L(+) lactic acid. Therefor no additional testing will be needed.

2. TEST PLAN FOR L(+) LACTIC ACID (CAS# 50-21-5)

	Information provided?	Data according GLP or OECD	Data Acceptable?	Additional tests required?
	Yes / No	Yes / No	Yes / No	Yes / No
Physical Chemical Data				
Melting Point	Yes	No	Yes	No
Boiling Point	Yes	No	Yes	No
Vapor Pressure	Yes	No	Yes	No
Partition Coefficient	Yes	No	Yes	No
Water Solubility	Yes	No	Yes	No
Environmental Fate				
Photodegradation	Yes	No	Yes	No
Stability in water	Yes	Yes	Yes	No
Transport between compartments	Yes	Yes	Yes	No
Biodegradation	Yes	Yes	Yes	No
Ecotoxicity				
Acute toxicity to aquatic plants	Yes	Yes	Yes	No
Acute toxicity to aquatic invertebrates	Yes	Yes	Yes	No
Acute toxicity to fish	Yes	Yes	Yes	No
Health endpoints				
Acute toxicity to mamals	Yes	Yes	Yes	No
Genetic toxicity in vivo	Yes	No	Yes	No
Genetic toxicity in vitro	Yes	No	Yes	No
Repeat dose toxicty	Yes	Yes	Yes	No
Reproductive toxicity	Yes	No	Yes	No
Developmental toxicity	Yes	Yes	Yes	No